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Anogenital Distance: Defining "Normal"

In their letter to *EHP*, McEwen and Renner (2006) dismissed the findings of Swan et al. (2005), who reported a significant relationship between a measure of anogenital distance (AGD) in boys and levels of phthalate metabolites in their mothers' urine during pregnancy. AGD is a sexually dimorphic index that, on average, is twice as great in males as in females, so it serves as a marker of proper male development. McEwen and Renner based their argument on an idiosyncratic form of logic. They asserted that

> All male infants evaluated in the study appeared normal … there is no evidence for potential adverse effect in the test population. … no conclusion can be drawn whether the reported values are normal or abnormal. The range of AGD values … likely represents typical biologic variation that would be expected to occur among normal study subjects.

McEwen and Renner seem to be wholly unfamiliar with the meaning of a modest or even a slight shift in the mean of an index that reflects the distribution of susceptibility in a population. I have pointed out (Weiss 1988) that even a 5-point (5%) reduction in mean intelligence quotient in a population of 100 million increases the number of individuals classified as retarded from 6 million to 9.4 million. It is this kind of relationship that eventually prompted the Centers for Disease Control and Prevention (CDC) to lower its definition of elevated lead risk levels in blood, set at 40 µg/dL in 1970, to 10 µg/dL in 1991 (CDC 1991). Bellinger (2006) put it this way:

> A small change in the mean signals predictable accompanying changes in the proportions of individuals in the source population who fall into the tails of the distribution, where individuals who meet diagnostic criteria are found. Thus, the importance of a shift in group mean lies not in what it indicates about the average change among members of the study sample, but what it implies about the changes in the tails of the distribution in the population from which the study sample was drawn.

He noted, based on Rose (1981), that in a population with a prevalence of clinically defined hypertension of 15%, a 5-mm reduction in mean systolic blood pressure would result in a 33% decrease in prevalence (Bellinger 2006). Epidemiologists recognize that a slight decrease in mean blood pressure in a population is translated into a major decrease in the incidence of serious cardiovascular events such as heart attacks.

We already know that shortened AGD at birth is one element, the leading edge, as it were, of the "phthalate syndrome" in rats, which is marked by testicular pathology, reduced spermatogenesis, hypospadias, and cryptorchidism, a compilation of signs indicating disordered male development that Sharpe (2001) and others have noted to be on the increase in industrialized nations. An almost imperceptible shift to a lower mean AGD in the human male would foreshadow a heightened prevalence of reproductive system dysfunction. Is that the connection now emerging in the clinic?

If McEwen and Renner's (2006) criteria for "normal" were to govern the way in which we define the health risks of lead exposure, we would be basing our criteria on the number of children brought into hospital emergency rooms with lead poisoning rather than on the threats it poses to their neurobehavioral development. No parent, and no community, would tolerate such a definition these days.

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Anogenital Distance: Bailey and Renner Respond

In his letter, Weiss misrepresents the arguments presented in our letter (McEwen and Renner 2006) regarding the study of Swan et al. (2005). We pointed out that a value for "normal" anogenital distance (AGD) is not known and that without this information, "abnormal" AGD values cannot be determined. Swan et al. (2005) measured AGD in a limited number of subjects (134 boys) who varied widely in age, height, and weight. This small sample size is inadequate to determine a normal AGD value, and there are no historical control data for AGD in male human infants using a definition of AGD comparable to the one used by Swan et al.

Although the significance of AGD values in humans, if any, is unknown, it is clear that a meaningful study with AGD as the end point of interest requires knowledge of normal values as a prerequisite. Further, the lack of knowledge of normal AGD values is only one of the significant limitations of the study by Swan et al. (2005); others were identified in our previous letter (McEwen and Renner 2006).

The authors are employed by advocacy groups that represent the interests of the cosmetic, toiletry, and fragrance industry.

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Mercury from Fish Does Not Reduce Children's IQs

Trasande et al. (2005) concluded that prenatal methylmercury (MeHg) exposure is reducing children's IQs (intelligence quotients), costing $8.7 billion/year. They achieved this high estimate *a*) by assuming that IQ reductions occur at MeHg exposures near or even below the 5.8 µg/L reference dose (RfD), although there is no evidence for IQ reductions even at much higher exposures; and *b*) by overstating by nearly a factor of three the fraction of newborns with MeHg exceeding the RfD. I believe that their analysis is flawed, invalid, and not appropriate as an input to policy decisions.

Trasande et al. (2005) assumed that 10% of newborns are exposed prenatally to MeHg exceeding the RfD. However, the appropri-

ate value is 3.6%. Trasande et al. made two errors. First, they used a lower RfD than 5.8 μg/L, based on the observed enrichment of MeHg in umbilical cord blood relative to maternal blood. However, the current RfD already accounts explicitly for this enrichment through an uncertainty factor of 3.15 applied to the benchmark dose lower limit [U.S. Environmental Protection Agency (EPA) 2001]. Second, they assumed that women 16–49 years of age measured during 1999–2000 accurately represented MeHg levels in pregnant women (Mahaffey et al. 2004). National Health and Nutrition Examination Survey (NHANES) data collected during 1999–2002 (Jones et al. 2004), available before Trasande et al. (2005) submitted their manuscript, show the 95th percentile MeHg level for pregnant women to be 32% below Trasande et al.'s value.

If any MeHg exposure above the RfD reduced IQ, there would still be cause for concern. However, there is no evidence for IQ reductions even at exposures several times the RfD.

Previous studies in the Seychelles Islands (Myers et al. 2003) and New Zealand (Crump et al. 1998) did not find IQ reductions at any MeHg exposure. A study in the Faroe Islands (Grandjean et al. 1999) did not measure IQ. Many children in these studies had prenatal MeHg exposures exceeding 10 times the RfD. The claim of IQ reductions in Americans is even weaker because Americans' MeHg exposures are far lower. Of 629 pregnant women measured by NHANES, the highest exposure was 3.7 times the RfD (Centers for Disease Control and Prevention 2005). Among those exceeding the RfD, 75% were below twice the RfD.

Trasande et al. (2005) cited results from the Faroe Islands (Grandjean et al. 1999) to claim IQ reductions, but this study is less compelling than the Seychelles study (Myers et al. 2003b) for assessing Americans' risks: *a*) the Seychellois are exposed to MeHg through ocean fish, similar to Americans, whereas the Faroese are exposed through whale meat (Myers et al. 2003b); *b*) the Seychellois are ethnically diverse, but the Faroese are homogeneously Scandinavian (Rice et al. 2003); and *c*) the Seychelles study used hair MeHg to measure exposure, and the Faroes study used cord blood. Hair MeHg has been calibrated with fetal brain levels, but cord blood has not (Cernichiari et al. 1995; Myers et al. 2003a).

Despite the advantages of the Seychelles study, Trasande et al. (2005) dismissed it, claiming that the National Research Council (NRC 2000) "opined that the most credible of the three prospective epidemiologic studies was the Faroe Islands investigation." In reality, referring to all three studies, the NRC (2000) concluded that "each of these studies was well designed and carefully conducted." Nevertheless, the NRC "concluded that a well-designed study with positive effects provides the most appropriate public-health basis for the RfD." The NRC thus excluded the Seychelles study not because of the quality of the study but because the study found that MeHg did not cause any harm.

Trasande et al. (2005) also made other errors:

- They claimed that the New Zealand study reported IQ reductions, citing Kjellstrom et al. (1986, 1989). However, they omitted Crump et al.'s (1998) reanalysis, coauthored with Kjellstrom, which superseded previous reports and found no IQ reduction.
- They claimed that the Seychelles study had only half the statistical power of the Faroes study. The studies actually have similar power (Myers et al. 2003; NRC 2000).
- They claimd the NRC concluded that MeHg reduces IQs even at exposures lower than the RfD. However, the NAS cautioned that the cohort studies were incapable of assessing effects of exposures near the RfD, because hardly any children had such low MeHg exposures (NRC 2000).

The weight of the evidence indicates that MeHg, even at exposures substantially greater than the highest U.S. levels, does not reduce children's IQ. The evidence against IQ reductions is particularly strong for MeHg exposures from fish.

Trasande et al. (2005) relied on mistaken assumptions regarding exposures to and effects of MeHg, and misinterpreted or omitted contrary evidence. Therefore, I consider their analysis to be fundamentally flawed and invalid.

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Children's IQs: Trasande et al. Respond

Schwartz makes a number of claims regarding our methodology (Trasande et al. 2005) that are inaccurate and based on a selective reading of the literature.

In our article (Trasande et al. 2005), we estimated the health and economic consequences of prenatal methylmercury (MeHg) exposure in the 2000 U.S. birth cohort. Our major findings were that at least 316,588 children in that birth cohort suffered IQ (intelligence quotient) loss of 0.2–24.4 points as a result of MeHg toxicity sustained *in utero*. This loss of intelligence causes diminished economic productivity that will persist, and this lost productivity is the major monetary consequence of methylmercury toxicity. We used the most up-to-date publicly available data on mercury exposures and health outcomes, applied a risk assessment approach developed by the National Research Council (NRC 1994), and made conservative assumptions throughout.

To compute decrements in IQ that resulted from prenatal mercury exposures, we used data from Mahaffey et al. (2004) on percentages of women of childbearing age in 1999–2000 with mercury concentrations ≥ 3.5, 4.84, 5.8, 7.13, and 15.0 μg/L. These

data most closely reflect exposure to women in the years 1999–2000, when toxicity to the developing brains of children in the 2000 birth cohort would have occurred. We then applied logarithmic and linear models to these data, and we calculated a range of IQ decrements for each subpopulation born with a cord blood mercury concentration > 5.8 μg/L. To assess a range of possible outcomes, we conducted a sensitivity analysis in which we applied a range of IQ decrements for each increase in mercury concentration. We described our methods in great detail (Trasande et al. 2005). Through this series of calculations, we generated upper and lower ranges of possible IQ decrements for each subpopulation among the most highly exposed children in the 2000 U.S. birth cohort.

In his letter, Schwartz asserts that it is impossible to impute effects on children's intelligence of prenatal exposures to mercury near the U.S. Environmental Protection Agency's (EPA) reference dose (RfD). In proffering this assertion, he appears to ignore a recent meta-analysis of the three studies that confirmed a dose–response relationship between low-level prenatal MeHg exposure and IQ (Cohen et al. 2005). A recent U.S. cohort study has also detected decrements in visual recognition memory among children exposed prenatally to MeHg (Oken et al. 2005).

Schwartz suggests that we should have used the U.S. EPA benchmark dose level (BMDL) of 58 μg/L as a cutoff. He apparently assumes that no injury occurs to fetal brains from exposure to MeHg below that level. That approach does not reflect biologic or epidemiologic reality. We based our selection of 5.8 μg/L as a no adverse effect level on the epidemiologic evidence, not on the U.S. EPA's regulatory documents (Budtz-Jorgensen et al. 2004; Grandjean et al. 1999; Kjellstrom et al. 1986, 1989). We relied especially upon the NRC's report on prenatal exposure to MeHg (NRC 2000), which concluded that the likelihood of subnormal scores on neurodevelopmental tests increased as cord blood mercury concentrations increased from levels as low as 5 μg/L. Methylmercury exposure has also been associated with persistent delays in peak I–III brainstem-evoked potentials at cord blood levels < 5 μg/L (Murata et al. 2004).

Schwartz misrepresents Crump et al.'s findings (1998), stating that they "superseded previous reports and found no IQ reduction." In fact, the NRC (2000) stated that Crump et al.

> reported nonsignificant results from a regression analysis on all the children in the New Zealand cohort, but [that these results became significant] after omission of a single child whose mother's hair Hg concentration was 86 ppm (4 times higher than that of the next highest exposure level in the study).

Schwartz misrepresents our characterization of the Seychelles Islands study (Landrigan and Goldman 2003; Myers et al. 2003), accusing us of stating that it had half the statistical power of the Faroe Islands study (Grandjean et al. 1999). In actuality, we stated that the Seychelles study "had only 50% statistical power to detect the effects observed in the Faroes" (Trasande et al. 2005). Schwartz asserts that the NRC's choice not to apply the Seychelles data in setting an RfD represents equivocation about the health effects of MeHg. In actuality, the NRC came to the same conclusion as we did: "[t]he weight of the evidence of developmental neurotoxic effects from exposure to MeHg is strong" (NRC 2000).

Recent work (Trasande et al. 2006) suggests that our calculation of the economic costs (Trasande et al. 2005) may, in fact, be an underestimate. The new study indicates that downward shifts in IQ are also associated with thousands of excess cases of mental retardation (defined as IQ < 70) in the United States each year. Care of these children is associated with needs for health care, special education, and other services that impose a great burden on society.

All of these adverse consequences can be prevented by prevention of prenatal exposure to MeHg.

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Erratum

A line of text was inadvertently omitted from the June 2006 Innovations article ("Plant vs. Pathogen: Enlisting Tobacco in the Fight Against Anthrax," *EHP* 114:A364–A367 [2006]). The last sentence on page A365 should read: "The current anthrax vaccine works on this very principle by introducing nonvirulent PA into the body so antibodies are created." *EHP* regrets the error.